Pharmacology of ACS

Introduction

Acute coronary ischemia treatment has some overlap with chronic coronary artery disease (CAD) therapies. We are not going to rehash the mechanisms of action, classes, and side effects that were already discussed in previous lessons. The goal of this lesson is to focus on the **acute management** of **acute disease**.

The mnemonic for the acute management of acute coronary syndrome is MONA-BASH-C. It has come under fire because the order of the letters seems to deprioritize the key features. We will forever teach this organizer because it is an **advanced organizer**, not a sequential checklist. It is so prevalent (well, we added the C to the original MONA-BASH) that everyone you work with will know about it. We will also explore some of the criticisms that have been received regarding some of the therapies. We finish the lesson with a deeper discussion of angioplasty, stenting, and coronary artery bypass grafting than was provided at the end of CAD #5: *Acute Coronary Syndrome*.

M	Morphine	Venodilator, pain control. Needing morphine portends more severe infarction.
O	Oxygen	Increase oxygen supply to ischemic tissue; may cause free radical formation.
N	Nitroglycerin	Venodilator, reduces the workload of heart, attempt SL 0.5 mg q5m ×3
A	Aspirin	Antiplatelet, ASA 325 mg oral or rectal on day of admission, 81 mg po qDay for life
B	β-Blocker	Reduces ventricular ectopies, prevents fatal arrhythmias
A	ACE inhibitor	Prevent remodeling of heart; afterload reduction
S	Statin	Long-term benefits of LDL reduction
H	Heparin	Therapeutic LMWH or heparin infusion to stabilize fibrin clot, prevent evolution
C	Clopidogrel	Clopidogrel load, 300 mg po, anticipating catheterization, stenting

Table 6.1: MONA-BASH-C
An advanced organizer for the treatment of patients with acute CAD. This is not a checklist or sequence of steps to follow. Like every other advanced organizer, it aids in providing a framework to understand and retain information.

Morphine

Morphine is used in the acute setting of myocardial infarction. It serves to alleviate pain and dilate veins. The dilation of veins leads to reduced venous return, therefore reducing the work of the heart, lessening demand. Alleviation of pain not only makes the patient feel better but also reduces the sympathetic surge that pain brings. Reduced sympathetic surge means less afterload (less α_1 vasoconstriction) and a slower heart rate (less β_1 tachycardia). Morphine is first in the mnemonic but is **not first-line therapy**. It has a purpose in the management of myocardial infarction, but it is the least helpful of them all.

Conveniently for our discussion, morphine is one of those treatments that have come under fire. A study demonstrated that (and we paraphrase), *the use of morphine in the setting of myocardial infarction is associated with worse outcomes*. But what many providers and learners heard was, *morphine causes worse outcomes*. The use of morphine in myocardial infarction is restricted to ongoing chest pain, pain that persists despite all the interventions you are about to learn. If the infarction is so bad that symptoms progress despite exhausting all medical therapies such that morphine is needed, you better believe there are going to be worse outcomes compared to a situation where someone's chest pain is alleviated with a spray of nitroglycerin. The morphine **does not cause** worse outcomes. The fact that the morphine is required portends a more severe infarct, and thus a worse outcome.

Morphine is a stand-in for any opioid. If you believe that morphine is bad and others aren't, use a different one. **Do not withhold pain medication from a patient with an acute injury who is in pain.** If you do, have a good reason for it. The diagnosis of myocardial ischemia is not a contraindication to morphine.

Oxygen

Oxygen is administered to increase oxygen delivery to ischemic tissue. It makes fundamental sense that if the tissue is hypoxemic, we could give more oxygen to lessen hypoxemia. **For any hypoxemic patient, give oxygen so that they are no longer hypoxemic.** If the sensor on their finger shows you a low oxygen level, you can bet that the obstructed coronary vessel has an even lower oxygen level. The vessels that aren't obstructed? They also have a lower than normal oxygen level. Never withhold oxygen from a hypoxemic patient.

What about patients who are not hypoxemic? The oxygen-carrying capacity of blood depends on hemoglobin. Once you get the oxygen saturation to 100%, all of the hemoglobin molecules are fully saturated. Adding more oxygen cannot add more oxygen to hemoglobin. But it can add oxygen to the plasma. To a very small extent, the partial pressure of oxygen dissolved in plasma contributes to oxygen delivery. If there is an underperfused heart, but blood flow is still getting there, and that heart is dying because of a lack of oxygen, it makes logical sense that you would want to increase the oxygen delivery however you could. This is faulty reasoning. **Oxygen free radicals and reperfusion injury are worse** than whatever benefit the extra oxygen was doing for the myocytes past the obstruction.

If the thrombosis is complete (100% occlusion), overoxygenating the blood that cannot reach the ischemic tissue does little for the ischemic tissue while the thrombus is there. If revascularized, the overoxygenated blood then arrives only to cause more oxygen free radicals. The **revascularization** (another word for reperfusion) of the obstructed vessel is the treatment that will save the myocardium. The side effect of revascularization is reperfusion injury. Increasing the oxygen in plasma increases oxygen free radicals and worsens reperfusion injury. If the patient isn't hypoxemic, you can let local reactive hyperemia take care of the reperfusion problem. Now that the stenosis is out of the way, with the restoration of perfusion, the endogenous mechanisms that govern blood flow can take back over.

So, some people got it in their heads to ask, "is oxygen good?" And to answer it, they did something stupid. A miserable recent study gave 8-LPM oxygen (which is a lot) to patients with normal saturation. No one gives 8 LPM to patients who are not hypoxemic. You start with a little oxygen (as part of the initial flurry of getting a chest pain patient admitted to a room and connected to all the things that need connecting) and then titrate the oxygen to effect (which may mean weaning to room air). But the study showed that too much of anything could be bad, including oxygen. No kidding. We already knew about oxygen free radicals and reperfusion injury. And the study excluded hypoxemic patients. But those who read the study (ahem, the abstract) concluded that *administering oxygen for myocardial infarction worsens infarct size and ventricular function.* NO! Intentionally overoxygenating someone who does not need oxygen supplementation, for longer than anyone would normally oxygenate someone, causes worsening infarct size and ventricular function.

The DET02X-AMI trial (which was done well) reported no benefit to giving oxygen to people with myocardial infarction who aren't hypoxemic. A much more logical conclusion from a more logical study. This validates current practice patterns—oxygen if needed, turn it off if not. Don't intentionally overoxygenate patients. Got it.

If a patient has a low oxygen level, give oxygen (agnostic to the diagnosis of myocardial infarction).

If a patient comes into the emergency department with substernal crushing chest pain, radiating up the jaw and down the arm, and they are pale, cool, and diaphoretic with a sense of impending doom, while the blood is drawn, clothes are removed, IV is placed, vital signs are obtained, and the 12-lead is brought around to the bedside, it is **okay to place a patient on nasal cannula oxygen**. Then in the ensuing hour, during which that patient has the attention of five-ish healthcare providers, one of those providers can decide how much oxygen to give. This complexity of oxygen delivery is included because of the prevalence and severity of CAD as well as the prevalence and severity of people chastising us for teaching oxygen use for myocardial infarction in the Clinical Sciences. The initial management should always be to place a patient on oxygen. The subsequent management will be to titrate that oxygen—up if hypoxemic, down if not.

You will not be asked this level of complexity on any exam. If you diagnose a coronary event, put the person on oxygen, and call your senior resident.

Here's the thing. There ARE times where blasting a patient with pure oxygen is a great thing to do, simply based on their diagnosis and not their oxygen level—a small pneumothorax. Oh, wait. I guess just one.

Nitroglycerin

Nitroglycerin induces smooth muscle relaxation. The main impact of this on myocardial ischemia is venodilation, reducing preload, and thereby demand. Its effects on coronary arteries are usually limited, especially if the thrombosis is 100% or the underlying atherosclerotic plaque is past critical stenosis (> 70%), and therefore, the artery is already maximally dilated.

Nitroglycerin is **absolutely contraindicated in an inferior infarct**. An "inferior infarct" is an infarct of the right ventricle. The right heart is preload dependent. Reducing venous return to a stunned, impaired, or infarcted right ventricle will critically drop the cardiac output and result in hypotension. **ST-segment elevation in II, III, and aVF** should prompt strict avoidance of nitrates (and other venodilators like morphine). ST-segment changes in leads II, III, and aVF with elevation of the cardiac enzymes (implying ischemia or strain of the right ventricle, although without complete transmural infarction) should also warrant avoidance of nitroglycerin. Oh, but . . . what else . . . ST-segment elevations in II, III, and aVF should be brought to the cath lab for revascularization!

Right coronary lesions are not common. Inferior infarcts are not the rule. Nitroglycerin is routinely taken by patients with stable angina. Nitroglycerin is routinely given to patients with CAD who present with acute chest pain. **Get the 12-lead first.** This is knowledge that every level of healthcare provider should be aware of. It is very easy to spray some nitroglycerin under the tongue of a patient with angina. If in the acute setting (i.e., anything other than stable angina), it can still be used, just with caution.

Aspirin

Aspirin is an antiplatelet. It is one mechanism to stabilize the clot. Stabilization means the clot will not enlarge or progress. ASA 325 mg is given orally or rectally in the first 24 hours as a core measure (hospitals are dinged on safety reports and financially for not doing). It has already been thoroughly discussed in CAD #4: *Chronic Ischemic Heart Disease Pharmacology*.

On licensing exams, the question will be "aspirin or nitroglycerin first?" For test-taking strategy, the answer is to give aspirin to a new presentation of angina in someone who doesn't have CAD and give nitroglycerin to a patient who has angina due to their CAD. In life, it is both, nearly at the same time, except where contraindicated.

β-Blockers

β-Blockers are chosen in chronic management for their ability to reduce the workload of the heart by blocking β_1 receptors. β-Blockers are indicated in all CAD patients.

β-Blockers prevent ventricular arrhythmias by reducing ventricular ectopy, preventing the most common cause of death within 24 hours of infarction.

In acute myocardial ischemia, the most common cause of death in the first 24 hours is **ventricular arrhythmia**. The subendocardial myocytes die first. The Purkinje fibers, the most sensitive pacemaker cells of the conduction system and the ones with the slowest phase 4, are in the subendocardial myocardium. Hypoxemia compromises the Na^+-K^+-ATPase. Resting membranes start more positive. **Ventricular ectopy** is the erroneous firing of the ventricular myocytes ahead of the SA node. The conduction system is unidirectional only because of how action potentials work and the refractory period that follows them. If either the pacemaker or non-pacemaker myocytes, both of which are dying, start shouting louder and faster than the SA node, **they become the pacemaker**. The conduction occurs backward. First the Purkinje fibers, then the bundle of His and the other side's Purkinje fibers (widening the QRS). The bundle of His travels up to the AV node, then from the AV node into the atria. Ventricular tachycardia and ventricular fibrillation occur because of ischemic tissue. β-Blockers decrease the effect of calcium channels, sodium channels, and funny channels, making it more difficult for tissue to depolarize erroneously.

β-Blockers should be given orally. If not possible, intravenously. The only reason not to give a β-blocker for myocardial infarction is if that myocardial infarction is accompanied by acute decompensated systolic heart failure or profound bradycardia. β-Blockers acutely depress the ejection fraction and can precipitate cardiogenic shock. At your level of training in the Basic Sciences, learn that **all heart attacks get β-blockers**.

ACE Inhibitors (and ARBs)

ACE inhibitors are good afterload reducers, decreasing the workload of the heart. They reduce preload over time by blocking aldosterone's effect. All good things for demand ischemia. In supply ischemia, ACE inhibitors **prevent the remodeling of the heart**. This was seen in CHF and chronic ischemic heart disease, and it is true in acute ischemic heart disease. Administration of an ACE inhibitor in the first 24 hours results in better prognosis, more preserved ventricular function, and reduced mortality. ACE/ARBs were discussed in detail in CAD #4: *Chronic Ischemic Heart Disease Pharmacology*.

Statins

The immediate effect of statins may be anti-inflammatory. If there is no contraindication to statin therapy, it should be started on the day of admission. The long-term effects are focused on preventing atherosclerotic progression and reducing the risk of the next thrombus, discussed in CAD #4: *Chronic Ischemic Heart Disease Pharmacology*.

This is one reason that some educators do not like MONA-BASH-C. The statin comes before heparin and clopidogrel in the mnemonic. We accommodate those concerns with the paucity of statin discussion in this lesson.

Heparin

As you are not expected to know the clotting cascade or its constituents at this point in your training, this discussion hopes to deliver the reasoning for heparin administration, even in the absence of the detailed mechanisms. If this gets a little too heavy, don't worry. We spend a lot of time on heparin's mechanism in Heme/Onc. Here, we want you to understand why we give it, not how it works.

Heparin binds and activates antithrombin-3, and antithrombin-3 inactivates factor 10 and factor 2 (thrombin). Factors 10 and 2 are critical in the formation of a fibrin thrombus. Heparin **stabilizes the clot** by preventing further activity of factor 10 and factor 2. Whatever fibrin thrombus had already been made is made, but new fibrin molecules will not be made or added to that fibrin thrombus.

Heparin is **not a thrombolytic**. It does not break down or remove the thrombus. But thrombi are constantly remodeling. The endogenous system degrades fibrin thrombi into split products. We give aspirin to silence platelet activation, which is required to generate the substrate used by the clotting cascade, to prevent any extension of the thrombus. Heparin works similarly, inhibiting enzymes that would lead to more fibrin formation. Antiplatelets, like aspirin, work on platelets, on primary hemostasis. Anticoagulants, like heparin, work on clotting factors, on **secondary hemostasis**.

In CAD #4: *Chronic Ischemic Heart Disease Pharmacology*, we told you definitively: antiplatelet for platelet arterial clot and anticoagulants for venous factor thrombi. So, what gives? For chronic management, that statement holds true, with few exceptions. For acute disease, because this ruptured-plaque-turned-thrombus is based on both platelets and factors, and because this event will kill myocardium, we go after both platelets and factors.

Any remodeling that happens, any fibrin that gets degraded, will stay degraded. This, like aspirin, **prevents the extension of the clot**. You're going to either help the patient resolve (or start to resolve) the clot using their endogenous system or help the patient stabilize the clot until revascularization.

Unfractionated heparin (UFH) is given as an infusion, and levels of factor Xa (activated factor 10) or PTT (a marker of coagulability) are assessed while the dose is adjusted. It can be turned off easily—literally because it is a continuous infusion, and figuratively because **protamine** works as an antidote. **Low molecular-weight heparin** (LMWH) can be given in therapeutic doses subcutaneously and does not require monitoring of labs. Protamine reverses LMWH less well than unfractionated, and since it is a one-time injection, it cannot be turned off.

For most clinical applications, LMWH is preferred to treat a non-STEMI myocardial infarction.

Revascularization

For a STEMI, there is only one treatment—revascularization. Revascularization of a STEMI is usually achieved by interventional cardiology—one vessel is reopened in an emergency with a door-to-balloon time of 90 minutes. The "door" is the patient's presentation to the hospital. The "balloon" is the angioplasty. Revascularization of a STEMI can also be achieved with thrombolytics (although this is rarely needed anymore in the United States). Separately, revascularization of symptomatic stenotic lesions and incomplete occlusions can be managed by interventional cardiology or cardiothoracic surgery. We talk about thrombolytics first in the context of STEMI. Then, because balloon angioplasty and stenting are the same procedure for STEMI and not-STEMI revascularization, we take a step back and consider the decision-making surrounding how the therapy is chosen in the not-STEMI situation.

Revascularization can be achieved with **thrombolytics** (tPA, streptokinase). Thrombolytics are only chosen if there is no center capable of interventional revascularization techniques within a **60-minute radius**. Thrombolytics come with a laundry list of serious caveats. For example, they are given intravenously, distributed everywhere in the body, so every clot that was made is unmade. **Bleeding risk is extraordinarily high.** Bleeding into the infarct can cause death. Bleeding into the brain can cause death. Bleeding anywhere can lead to exsanguination. tPA is an option. Reach for it only in very specific situations—when the patient is definitely experiencing a STEMI and has no contraindications, and an interventionalist is unavailable. Do not memorize the contraindications for tPA; there are written protocols at every station where it can be administered. Checklist medicine makes for weak providers, and checklist procedures make for strong outcomes. The administration of tPA is one of those checklist procedures.

A **diagnostic angiogram** is one where the femoral or radial artery is penetrated with a catheter. The wire is fed to the coronary ostia, but not inside. The dye is injected, and a video is captured. Where the dye goes is where a vessel is patent. Where the dye fails to go but should go is an occluded artery. Where the dye narrows but shows flow on the other side is a stenotic lesion. The cardiologist can assess the number and severity of lesions. What happens after the diagnostic angiogram depends on the number and size of lesions. The wire does not go into the coronaries. Any cardiologist can perform this procedure.

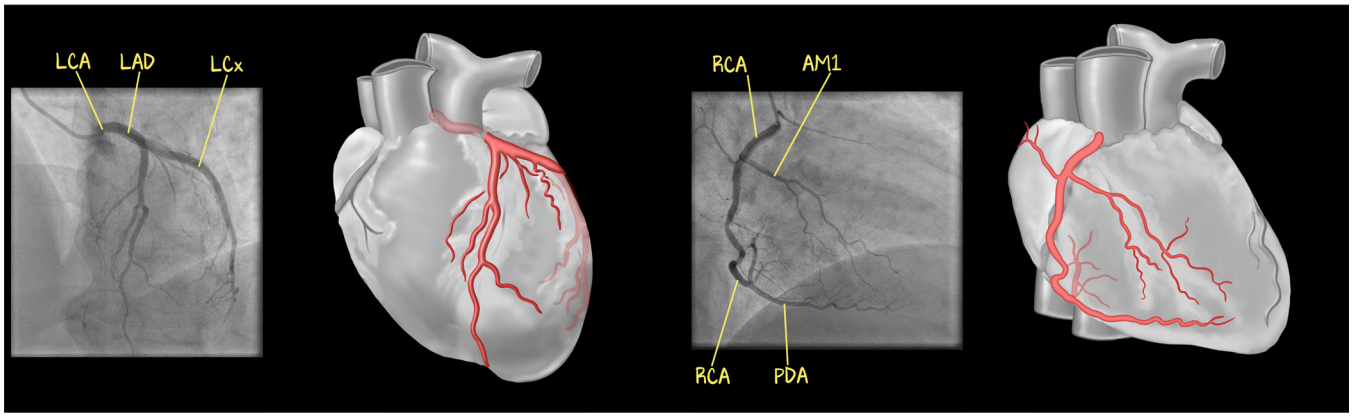

Figure 6.1: Angiography
Angiography enables visualization of the lumens of the arteries. Cardiologists are trained in interpreting the image they see with the camera angled in various directions. You can't see the heart itself, although you can infer it if given the correct perspective.

Percutaneous coronary intervention (PCI), also referred to as a left heart catheterization, also known as angioplasty with stenting, has two primary indications. The first is the alleviation of a STEMI. Because it is rare for more than one vessel to thrombose simultaneously, the PCI goal in the setting of STEMI is to alleviate the **one thrombosed vessel**. If other stenotic lesions are identified, there is a decision to make. That decision is the same as if a diagnostic angiogram were performed outside the setting of a STEMI, where revascularization is needed emergently. After the STEMI is taken care of (or in the outpatient setting), PCI is the intervention of choice when there are **few vessels affected** (1 or 2) and those vessels are **not large** (not LAD, LCx, RCA).

PCI can be angioplasty alone, angioplasty with a bare-metal stent, or angioplasty with a drug-eluting stent. **Angioplasty** alone is smooshing the atherosclerotic plaque against the vessel wall to get rid of the clot and hope that you will get the plaque. But without anything in place, the plaque just falls back into its previous position. Recurrence of atherosclerotic **stenosis**. With **angioplasty and** a **bare-metal stent,** you smoosh the plaque out of the way and leave a metal mesh in place that keeps the plaque smooshed. The lumen is restored, and the blood flow is normal. But metal is seen by the tunica media as just another lipid core. **Neointimal hyperplasia** is a special, rapid form of in-stent stenosis. The tunica media overgrows the stent, and a new stenotic lesion develops. To eliminate that pesky problem, **drug-eluting stents** are now used. With these stents, the angioplasty (smooshes the plaque) and mesh (keeps it smooshed) are just like those in a bare-metal stent, but the drug-eluting stent elutes a drug that prevents neointimal hyperplasia.

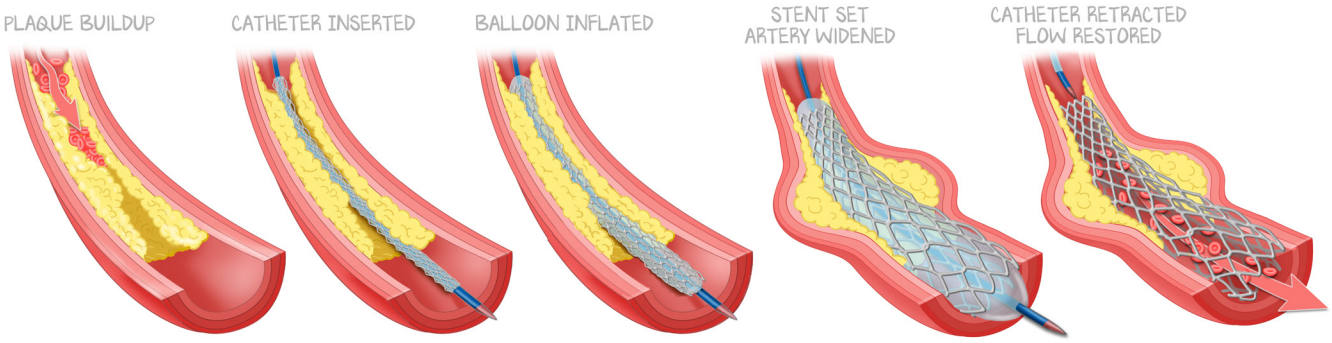

Figure 6.2: Revascularization With Stent
Either at critical stenosis or in acute rupture and thrombosis, there is a lesion that needs fixing. A catheter with an uninflated balloon is passed across the lesion. The balloon is deployed, compressing the plaque, keeping it out of the lumen. A stent is left in place to prevent the old stenotic plaque from rebounding into the lumen. Drug-eluting stents prevent the slowly developing problem of neointimal hyperplasia (in-stent stenosis). DAPT is used to reduce the risk of in-stent thrombosis (akin to rupture and thrombosis) caused by the platelets in the bloodstream colliding with the metal stent.

But wait, there's more. If there is no metal left behind (angioplasty), there is nothing for passing platelets to identify. Thus, there is no risk of **in-stent thrombosis** (because there is no stent). Bare-metal stents have an increased risk of in-stent thrombosis, and drug-eluting stents have the highest risk. To prevent in-stent thrombosis, we use **dual-antiplatelet therapy** (DAPT). The higher the risk for in-stent thrombosis, the longer the duration.

In-stent stenosis is the slowly developing plaque on top of the stent, also called neointimal hyperplasia. **In-stent thrombosis** is like plaque rupture and thrombosis, only the thrombosis happens because of the stent. You put the patient on DAPT (aspirin + ADP antagonist), which they take every day by mouth to reduce thrombosis. The drug-eluting stent has the drug in it to prevent stenosis.

	RECURRENCE	IN-STENT STENOSIS	IN-STENT THROMBOSIS
Angioplasty alone	High	None	None
Angioplasty + BMS	Low	High	Moderate
Angioplasty + DES	Low	Low	High

Table 6.2: Outcome Comparison Among Revascularization Treatments
BMS, bare-metal stent; DES, drug-eluting stent.

For all patients without special considerations, angioplasty with a drug-eluting stent followed by lifelong therapy with DAPT is preferred. In PCI, the wire is inserted into the coronary vessel, in which the balloon is inflated. The risk of this procedure is that instead of staying in the vessel, the wire could **perforate** the coronary artery, necessitating surgery. PCI is performed by interventional cardiology, which requires a minimum of 1 additional year of fellowship to perform (after 3 years of internal medicine residency and 3 years of cardiology fellowship).

Choosing Wisely campaigns recommends that intervening on nonocclusive lesions is not appropriate. If < 70% stenosis is seen on an angiogram and it is asymptomatic, do not stent. Stent the critical stenosis lesion. Stent the thrombosed lesion.

For those with **many affected vessels** (3+) or a **left mainstem equivalent**, the treatment is coronary artery bypass grafting (CABG). This is open-heart surgery. The largest affected artery is connected to the **left internal mammary artery** (LIMA). There is only one LIMA (also known as the left internal thoracic artery, LITA). The one LIMA can be used only one time. The LIMA is used for the largest affected artery because it is an artery and can tolerate the pressures of ventricular contraction. The vessel bypassed by the LIMA will fill in **systole**. All other vessels are bypassed by harvesting the **saphenous vein,** using strips of it to connect the unoccluded proximal segment (aorta or left coronary) to the segment distal to the occlusion. Over time, the vein, experiencing diastolic pressures of the systemic vasculature (the ostia fill during diastole), will arterialize, developing a thick tunica media with elastin fibers and smooth muscle cells. The vein acts as a conduit at first, then adapts to the increased pressures.

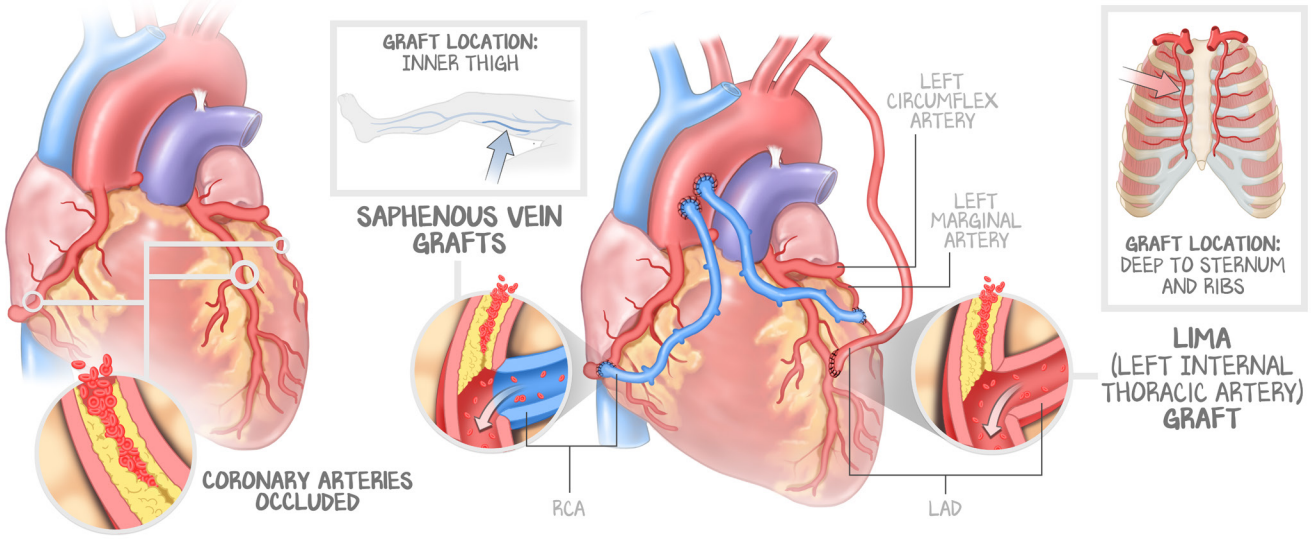

Figure 6.3: Revascularization With CABG
Multiple coronary arteries need fixing. During the procedure, the saphenous vein is harvested from the patient as an autologous transplant. The LIMA is dissected and connected to the largest affected artery—in this case, the distal LAD. The remaining lesions are bypassed using the saphenous vein grafts. They are sutured into the aorta near the coronary ostia and then sewn into the vessels distal to their lesions. The vessels proximal to the stenosis receive blood from the coronary arteries as normal. The vessels distal to the stenosis receive blood from the grafts.

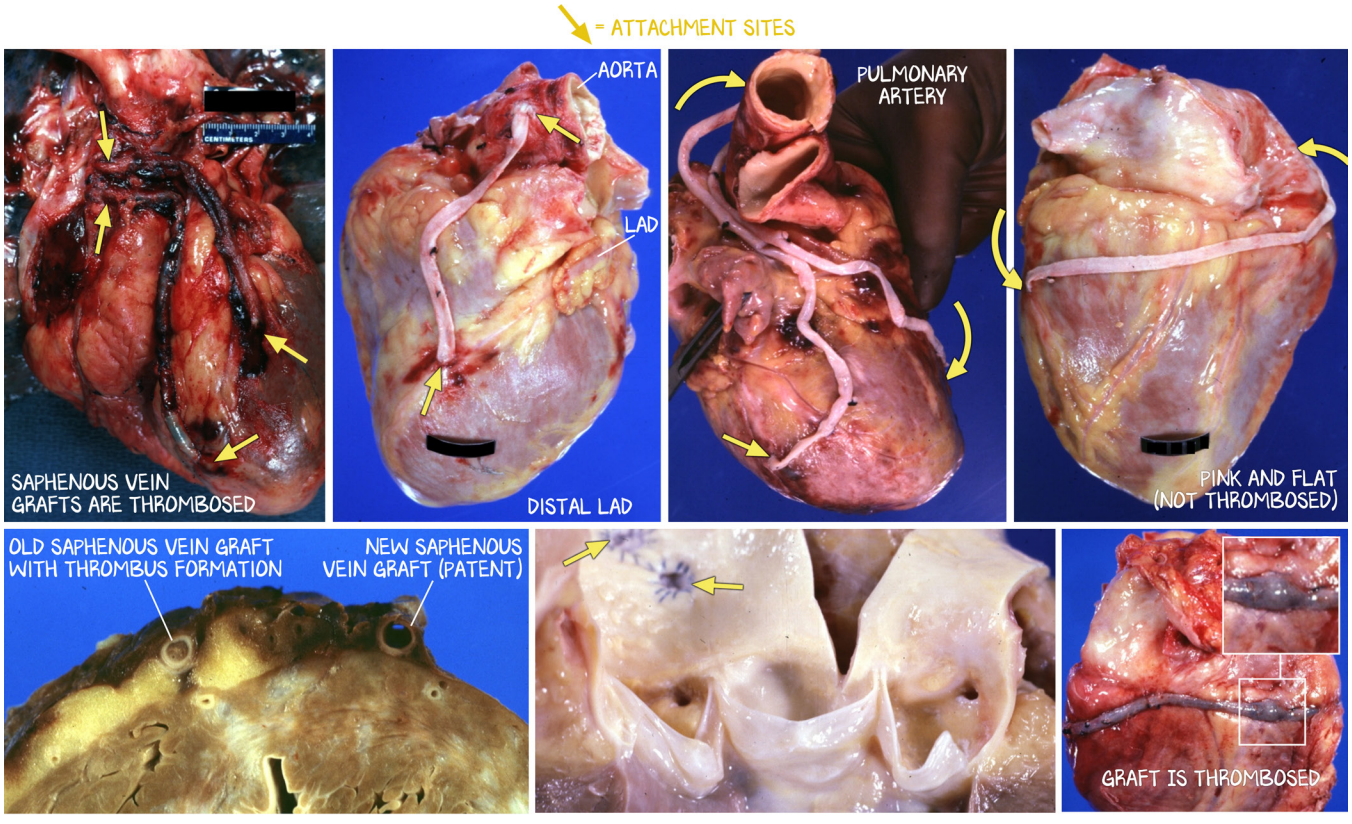

Figure 6.4: Actual CABGs

All patients with CAD of any severity or kind should be kept on **lifelong dual-antiplatelet therapy.** DAPT should only be discontinued after the minimum duration has passed for the stent they had placed AND if there are bleeding complications due to the antiplatelet medication. Life-threatening hemorrhage in a patient with a recently placed stent is not something you'll need to consider until much farther along in your career.

STENT	ANTIPLATELET THERAPY	MINIMUM DURATION	INTENDED DURATION	RECURRENCE
Angioplasty alone	ASA + Clopidogrel	N/A	Life	Highest
Bare-metal stent	ASA + Clopidogrel	1 month	Life	Moderate
Drug-eluting stent	ASA + Clopidogrel	1 year	Life	Lowest
CABG	ASA + Clopidogrel	N/A	Life	N/A
No intervention but CAD	ASA + Clopidogrel	N/A	Life	N/A

Table 6.3: Dual-Antiplatelet Therapy
This is used to illustrate the overall theme of CAD management—DAPT for everyone.

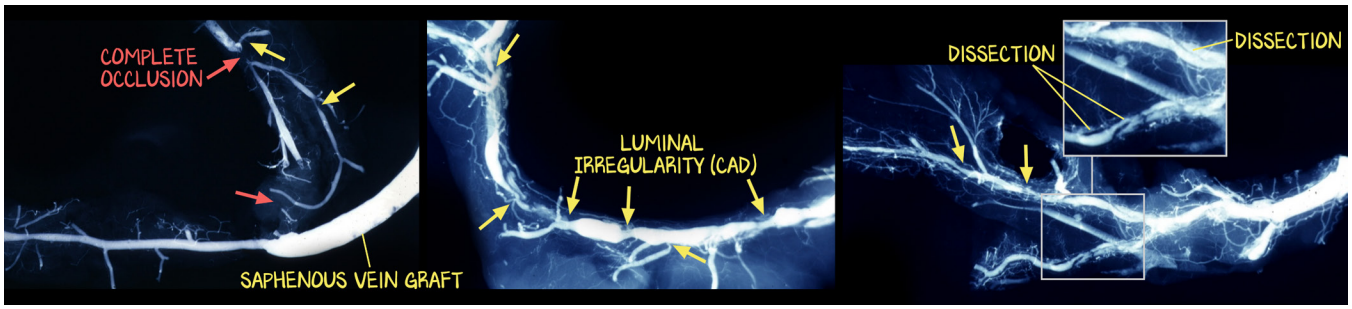

Figure 6.5: Postmortem Angiography of Disease
The names of the arteries shown are being withheld so that you focus on their features. The leftmost artery has two total occlusions and evidence of a saphenous vein graft. The middle artery has numerous luminal irregularities. Vessels only get smaller the further down the arterial tree they are. Most specifically, the origin of an artery should be as wide as the artery. Finding a slender branchpoint (as in the arrow at the bottom) that then widens is evidence of luminal obstruction. The artery on the right demonstrates coronary artery dissection due to atherosclerosis.